contd. C6

aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

$R^{12}$ and $R^{13}$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

$R^4$ and $R^5$ or $R^5$ and $R^6$ may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring.

## REMARKS

The Examiner has indicated that the claims allegedly encompass 7 different inventions and has required election of one the inventions under 35 U.S.C. 121.

Applicants' Election

Applicants hereby elect to prosecute, with traverse, the claims encompassed by Group I, claims 1-9, 11-16, 18-37, and 41-45, drawn to compounds, compositions, method of use and process of preparing the compounds of formula I, where one of D, E, F, and G is nitrogen and the others are carbon. Applicants have canceled claims drawn to the non-elected subject matter, as discussed below.

The examiner has also required the election of a single species. Applicants hereby *provisionally* elect to prosecute the compound 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid. Support for the elected species is set forth, *inter alia*, in originally filed claim 18.

Applicants' Traversal

Applicants respectfully traverse the requirement for restriction between invention Groups I-V. Where there is not a serious burden on the Examiner, restriction is not proper (*see* MPEP 803). Specifically, in the present case, there would not be a serious burden on the Examiner if

restriction is not required between the groups as represented by the claims. It would not be unduly burdensome for the Examiner to search simultaneously for compounds which differ only in the positions of nitrogen and carbon in one of two fused rings. On this basis, reconsideration and withdrawal of the requirement are respectfully requested.

Applicants' Amendments

Claims 10, 17, and 38-40 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. By canceling the non-elected claims, Applicants make no admission as to the patentability of the subject matter thereof. Applicants reserve the right to file continuation, divisional, or continuation-in-part applications drawn to the subject matter of the non-elected claims, as well as any other subject matter disclosed in the present application which is not encompassed by the elected claims.

Claims 1 and 41 have been amended to reflect Applicants' election. The amendments clearly set forth the elected subject matter where only one of D, E, F, and G in the compound of formula I can be nitrogen and the rest are carbons. The amendments to the claims are supported by the description and claims as originally filed.

No new matter has been added by these amendments. Applicants have attached herewith as Appendix A the text of the pending claims following the present amendments for the Examiner's convenient reference.

## CONCLUSION

In view of the above, Applicants respectfully submit that the claims are in condition of allowance. Applicants respectfully request that the Application be allowed and passed to issue. Applicants have enclosed a petition for a one month extension of time and a check for $110.00. If this amount is incorrect, please charge or credit Lyon & Lyon Deposit Account No. 12-2475 for the appropriate amount. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (858) 552-8400.

Respectfully submitted,

LYON & LYON, LLP

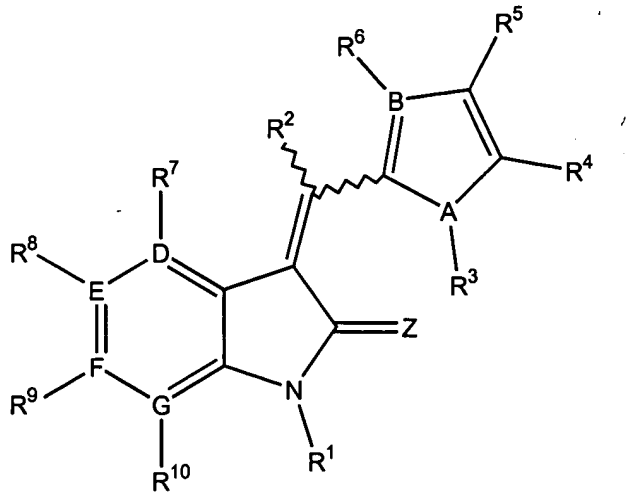
Dated: January 18, 2000

Charles S. Berkman
Attorney for Applicants
Reg. No. 38,077

CSB:skt
633 West Fifth Street, 47th Floor
Los Angeles, California 90071-2066
Telephone: (858) 552-8400

# APPENDIX A
## CURRENTLY PENDING CLAIMS

1. A 3-heteroarylideneazaindolin-2-one compound having the following chemical structure:




wherein,

A is selected from the group consisting of nitrogen, oxygen and sulfur and it is understood that when A is oxygen or sulfur, $R^3$ does not exist and there is no bond;

B, D, E, F and G are independently selected from the group consisting of carbon and nitrogen wherein only one of D, E, F and G is nitrogen and the other of D, E, F, and G are carbon, and it is understood that when B, D, E, F or G is nitrogen, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$, respectively, do not exist and there is no bond;

Z is selected from the group consisting of oxygen, sulfur and $NR^{11}$ wherein,

$R^{11}$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

$R^1$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, trihalomethanecarbonyl, sulfonyl, trihalomethanesulfonyl, C-carboxyl, O-carboxyl, C-amido, and guanyl;

$R^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and halogen;

when A is nitrogen,

$R^3$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

$R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

$R^{12}$ and $R^{13}$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

$R^4$ and $R^5$ or $R^5$ and $R^6$ may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring;

and the physiologically acceptable salt and prodrugs thereof.

2. The compound, salt or prodrug of claim 1 wherein $R^1$ is selected from the group consisting of hydrogen and alkyl.

3. The compound, salt or prodrug of claim 2 wherein Z is oxygen.

4. The compound, salt or prodrug of claim 3 wherein $R^2$ is hydrogen.

5. The compound, salt or prodrug of claim 4 wherein $R^7$, $R^8$, $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkoxy, thioalkoxy, nitro, amino and N-amido.

6. The compound, salt or prodrug of claim 5 wherein D is nitrogen.

7. The compound, salt or prodrug of claim 5 wherein E is nitrogen.

8. The compound, salt or prodrug of claim 5 wherein F is nitrogen.

9. The compound, salt or prodrug of claim 5 wherein G is nitrogen.

11. The compound, salt or prodrug of claim 1 wherein A is nitrogen.

12. The compound, salt or prodrug of claim 11 wherein $R^3$ is selected from the group consisting of hydrogen and alkyl.

13. The compound, salt or prodrug of claim 12 wherein $R^4$, $R^5$ and $R^6$ are independently selected from the groups consisting of hydrogen, alkyl, C-carboxy and a six-member cycloalkyl ring formed by the combination of $R^4$ and $R^5$.

14. The compound, salt or prodrug of claim 12 wherein $R^4$ and $R^6$ are alkyl and $R^5$ is hydrogen.

15. The compound, salt or prodrug of claim 1 wherein A is sulfur.

16. The compound, salt or prodrug of claim 15 wherein $R^4$, $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkynyl, aryl,

heteroaryl, aryloxy, thioalkoxy, halo, nitro, trihalomethane-carbonyl and an aryl ring or a heteroaryl ring formed by the combination of $R^4$ and $R^5$.

18. A compound selected from the group consisting of 3-(3,5-dimethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-(3,5-diethyl-1H-pyrrol-2-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-(3H-imidazol-4-ylmethylene)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one, 3-[4-methyl-5-(2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid, and 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-pyrrolo[2,3-b]pyridin-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid.

19. A pharmacological composition of said compound, salt or prodrug of any one of claims 1-18.

20. A method for the modulation of the catalytic activity of a protein tyrosine kinase comprising administering said compound, salt of prodrug of any one of claims 1-18 to said protein tyrosine kinase.

21. A method for treating or preventing a protein tyrosine kinase related disorder in an organism comprising administering a therapeutically effective amount of said pharmacological composition of claim 19 to said organism.

22. The method of claim 21 wherein said protein tyrosine kinase related disorder comprises a cell proliferation, differentiation or growth disorder.

23. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a PDGF related disorder.

24. The method of claim 23 wherein said PDGF related disorder comprises cancer.

25. The method of claim 24 wherein said cancer comprises blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer or prostate cancer.

26. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a EGF related disorder.

27. The method of claim 26 wherein said EGF related disorder comprises cancer.

28. The method of claim 27 wherein said cancer comprises squamous cell carcinoma, astrocytoma, glioblastoma, head and neck cancer, lung cancer and bladder cancer.

29. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a IGF related disorder.

30. The method of claim 29 wherein said IGF related disorder comprise cancer.

31. The method of claim 30 wherein said cancer comprises breast cancer, small-cell lung cancer, and gliomas.

32. The method of claim 22 wherein said cell proliferation, differentiation or growth disorder comprises a met related disorder.

33. The method of claim 32 wherein said met related disorder comprises cancer.

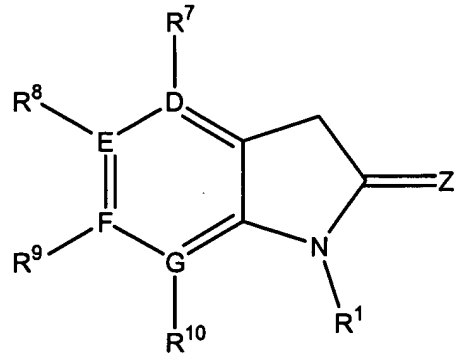
34. The method of claim 33 wherein said cancer comprises colorectal cancer, thyroid cancer, pancreatic and gastric carcinoma, leukemia and lymphoma, Hodgkin's disease and Burkitts disease.

35. The method of claim 21 wherein protein tyrosine kinase related disorder comprises arthritis, diabetic retinopathy, restinosis, hepatic cirrhosis, atherosclerosis, angiogenesis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection, autoimmune disease, diabetes or hyperimmune disorders.

36. The method of claim 21 wherein said organism is a mammal.

37. The method of claim 36 wherein said mammal is a human.

41. A method for synthesizing an indolinone compound of any one of claims 1-17 comprising the step of reacting a first reactant with a second reactant in a solvent and in the presence of a base at elevated temperatures, wherein said first reactant is an azaindolin-2-one having the structure set forth in formula 2

(2) 


wherein

D, E, F and G are independently selected from the group consisting of carbon and nitrogen wherein only one of D, E, F and G is nitrogen and the other of D, E, F, and G are carbon, and it is understood that when D, E, F or G is nitrogen, $R^7$, $R^8$, $R^9$ and $R^{10}$, respectively, do not exist and there is no bond;

$R^7$, $R^8$, $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino, and $-NR^{12}R^{13}$, wherein

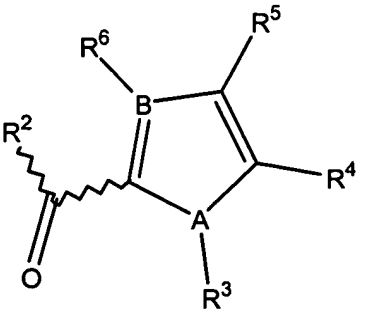
$R^{12}$ and $R^{13}$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

Z is selected from the group consisting of oxygen, sulfur and $NR^{11}$ wherein,

$R^{11}$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl; and

$R^1$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, trihalomethanecarbonyl, sulfonyl, trihalomethanesulfonyl, C-carboxyl, O-carboxyl, C-amido, and guanyl;

and wherein said second reactant is an acyl compound having the structure set forth in formula 3

(3) 


wherein

A is selected from the group consisting of nitrogen, oxygen and sulfur and it is understood that when A is oxygen or sulfur, $R^3$ does not exist and there is no bond;

B is selected from the group consisting of carbon and nitrogen and it is understood that when B is nitrogen, $R^6$ does not exist and there is no bond;

$R^2$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl and halogen;

when A is nitrogen,

$R^3$ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxy, alkoxy, aryloxy, carbonyl, C-carboxyl, O-carboxyl, C-amido, guanyl, sulfonyl and trihalomethanesulfonyl;

$R^4$, $R^5$, and $R^6$ are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, S-sulfonamido, N-Sulfonamido, trihalomethanesulfonyl, carbonyl, C-carboxyl, O-carboxyl, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, guanyl, guanidino, ureido, amino and $-NR^{12}R^{13}$, wherein

$R^{12}$ and $R^{13}$ are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, sulfonyl and, combined, a five- or six-member heteroalicyclic ring containing at least one nitrogen; and,

$R^4$ and $R^5$ or $R^5$ and $R^6$ may combine to form a six-member cycloalkyl, aryl, heteroaryl or heteroalicyclic ring.

42. The method of claim 41, wherein said first reactant is an azaindolin-2-one selected from the group consisting of the indole portion of the compounds listed in Table 1.

43. The method of claim 41, wherein said second reactant is an acyl compound selected from the group consisting of the acyl portion of the compounds listed in Table 1.

44. The method of claim 41, wherein said base is selected from the group consisting of a nitrogen base and an inorganic base.

45. The method of claim 41, wherein said solvent is selected from the group consisting of water, an alcohol, and dimethylformamide.